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## Diagnosis of Pheochromocytoma and Paraganglioma

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### Abstract

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors that usually present with classic paroxysmal symptoms including headache, palpitation, anxiety and diaphoresis. Adrenergic and noradrenergic tumors are two biochemical types of PPGLs. The biochemical phenotype is important for predicting the location of the tumor, and the type of germline mutation. It is challenging for the clinician to diagnose this deadly disease due to the conditions with these non-specific symptoms. PPGLs are diagnosed with biochemical confirmation of catecholamine excess followed by anatomical localization. Biochemical testing should be considered for patients having paroxysmal symptoms or signs indicating catecholamine excess, paradoxical blood pressure response, resistant hypertension, incidental adrenal mass, previous diagnosis of PPGLs, family history of PPGLs, and syndromic features suggesting PPGLs. Initial biochemical tests for PPGLs are plasma free or urinary fractionated metanephrines. To get an accurate biochemical testing clinicians must obey rules for blood and urine sampling correctly. Anatomic and functional imaging modalities are used as needed. Genetic analysis by accredited laboratories is recommended for all patients. In this chapter, we review the diagnosis of PPGLs with a focus on clinical presentation, biochemical testing, imaging procedures and genetic analysis, guidance on when to perform case detection testing considering current case detection tests.

### Introduction

Pheochromocytomas and paragangliomas (PPGLs) are rare and potentially fatal tumors. It is very important to make accurate diagnosis or exclude diagnosis due to the high mortality and morbidity if left untreated and results in cure if timely treated. Also for some familial cases, establishing a correct diagnosis may ensure early recognition and treatment of affected family members. Additionally the malignancy prevalence of these tumors varies between 10-17% so case detection is important to plan the extent of the treatment [1].

Among patients tested for PPGLs, a small number of patients (less than 1%) actually have the tumor but real incidence may be higher because many of these tumors are missed or diagnosed during autopsy [2]. Pheochromocytoma was diagnosed in 4 out of 8486 autopsies (0.05%) [3]. The tumor is frequently considered but rarely found.

### Diagnosis of Pheochromocytomas and Paragangliomas

#### Signs and Symptoms

The key point for the diagnosis of PPGLs is to suspect the presence of the disease. Patients may present in a variety of non-specific signs and symptoms which is associated with catecholamine hypersecretion mimicking disorders such as renovascular or essential hypertension, sleep apnea, anxiety, mastocytosis, hyperthyroidism, and hypogonadal hot flashes. Some patients may exhibit no symptoms while others present in life-threatening clinical situations such as acute myocardial infarction or stroke. The classical triad of PPGLs is headache, palpitation and excessive sweating, occurring with variable frequency and duration either spontaneously or after physical or chemical triggers, such as exercise, micturition, general anesthesia and medications (e.g.,  $\beta$ -adrenergic receptor blockers, monoamine oxidase inhibitors, corticosteroids). Many patients may also experience hypertension either which may be sustained or paroxysmal. Increased risk of cardiovascular events is not only due to the high blood pressure but also to prolonged exposure to the toxic effects of catecholamines [4].

Other symptoms are tremors, weakness, fatigue, pallor, anxiety, nervousness, nausea, vomiting, and fever. Additionally affected patients may experience cerebrovascular accidents, transient ischemic attacks, acute respiratory distress syndrome, impaired renal function, acute tubular necrosis, and hypertensive nephrosclerosis. Rarely, new onset secondary diabetes may be seen in younger patients free of any risk factors [5].

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## Biochemical testing

The Endocrine Society recommends the measurement of plasma-free metanephrines and urinary fractionated metanephrines by using liquid chromatography with mass spectrometric or electrochemical methods as the initial diagnostic laboratory testing for PPGLs [1]. Measurement of catecholamines in plasma or urine is not an effective method because these tumors don't produce catecholamines continuously so it can cause false negative results during the periods of low catecholamine release. On the other hand, plasma or urine metabolites, i.e., metanephrines and normetanephrines, are produced continuously by membrane-bound catechol-O-methyltransferase (COMT) and can be detected consistently elevated in patients with biochemically active tumors [6].

Several studies have shown that plasma free metanephrines have high sensitivity for diagnosis of PPGLs (90-100%) [1,7,8]. Specificity of plasma free metanephrines varies between 79.4-97.6 %. Although urinary vanil mandelic acid (VMA) has high specificity, its use as an initial test is not recommended because of its low sensitivity [9].

Plasma methoxytyramine, an O-methylated metabolite of dopamine, may provide an additional benefit for the detection of PPGLs especially for head and neck paragangliomas. This biomarker can be used for dopamine-secreting tumors [10]. Also it is useful together with SDH mutation status, tumor size and location, for assessing the likelihood of malignancy [11].

Some factors may influence the levels of plasma free metanephrines. Smoking may increase them. It is recommended not to smoke for at least 4 hours before sample collection. Local anesthetics, lidocaine, halothane, MAO inhibitors, cocaine, and epinephrine-like drugs can interfere with the levels of plasma free metanephrines. Stressful illness, renal failure, and cold-associated increased sympathetic nerve activity may cause misleading elevations in plasma free metanephrines. Food intake and physical exercise also do so. Use of sympathomimetics and stimulants such as caffeine can increase catecholamine release therefore such phenomenon can be minimized by avoiding these agents before sample collection. Seated sampling may potentially cause misdiagnoses associated with sympathoadrenal activation and therefore preferably blood samples should be drawn from the patient in the supine position. If a positive test result is detected after the collection in the seated position, the test should be repeated in the supine position to rule out false positive cases. Urinary fractionated metanephrines can be preferable in low risk populations for centers unable to provide the supine position. Clonidine suppression test may help to distinguish true positive from false positive elevations. Another option to exclude false positive elevations of plasma metanephrines is measurement of chromogranin and urinary free metanephrines. Test results under the upper limit of normal for plasma free metanephrines exclude almost all cases of PPGLs except microscopic recurrent tumors, incidentally discovered small tumors (<1 cm), patients with hereditary predisposition to PPGLs, tumors producing only dopamine, head and neck non catecholamine-synthesizing paragangliomas and paragangliomas. Since plasma free and urinary fractionated metanephrines have high negative predictive value, further investigations are not needed for patients with test results falling within the reference intervals [12].

Chromogranin A (CgA) is a soluble acidic protein that is commonly secreted and stored with catecholamines by the chromaffin cells. Although it is a non-specific biomarker of neuroendocrine tumors, its elevated levels are found in 91% of PPGL cases and can be used for disease monitoring purposes [5]. In combination with plasma normetanephrine, CgA enhances tumor detection by 22% in evaluation of succinate dehydrogenase (SDH) B-related PPGLs [13].

PPGLs can also secrete some peptide hormones other than catecholamines, including calcitonin, cytokines, parathyroid hormone-related peptide, erythropoietin, neuropeptide Y, and neuron-specific enolase and some of them may cause different clinical symptoms. For example ACTH production by the tumor cells can cause Cushing's syndrome [14].

## Genetic testing

Accumulating evidence in molecular research suggests that at least 30-40% of PPGL arise in the context of hereditary disease. A positive family history, multifocal presentation, bilateral adrenal involvement, young age at diagnosis or syndromic signs are main features prioritizing patients for testing [15]. However, germline mutations in sporadic PPGLs were found 11-13% in a study including only patients who had three or four criteria stated as absence of bilateral involvement, metastatic disease, syndromic signals and family history [16]. Therefore, genetic testing is a critical component of the clinical evaluation of patients diagnosed with PPGLs and current guidelines recommend genetic testing for all patients with PPGLs.

According to the literature, there are 17 PPGL susceptibility genes named as neurofibromatosis 1 (*NF1*), rearranged during transfection (*RET*), von Hippel-Lindau (*VHL*), succinate dehydrogenase D (*SDHD*), succinate dehydrogenase C (*SDHC*), succinate dehydrogenase B (*SDHB*), EGL nine homolog 1 (*EGLN1/PHD2*), kinesin family member 1B (*KIF1B*), succinate dehydrogenase assembly factor 2 (*SDH5/SDHAF2*), isocitrate dehydrogenase (*IDH1*), transmembrane protein 127 (*TMEM127*), succinate dehydrogenase A (*SDHA*), myc-associated factor X (*MAX*), hypoxia-inducible factor alpha (*HIF2α*), fumarate hydratase (*FH*), malate dehydrogenase 2 (*MDH2*) and BRCA-1 associated protein-1 (*BAP1*). However, the role of somatic or germline mutations in few of the latter need confirmation in further studies.

35% and 15% of PPGLs have germline and somatic mutations, respectively. In addition to this high frequency, the detection of such fatal hereditary disease for at-risk families justifies the evaluation of genetic examination for each PPGL patient despite financial cost considering the effect of the result on management. Nockel et al investigated the effect of preoperative genetic testing in PPGLs and found that preoperative knowledge of the germline mutation status affects the extent of adrenalectomy and the surgical approach [17]. However, the availability of molecular tests, resources and an accredited laboratory is needed. Additionally, with the rise of a panel approach to molecular examining, it is recommended to prioritize molecular testing according to young age, positive family history, syndromic or metastatic presentation, multifocal involvement, bilateral adrenal disease and catecholamine biochemical phenotype. The mode of inheritance is most commonly autosomal-dominant and related diseases are NF-1, multiple endocrine neoplasia type 2 (MEN2), VHL syndrome, renal cell carcinoma with SDHB mutation, Carney triad, Carney Stratakis syndrome [18]. Evaluation of NF-1 gene is complex and testing is possible only in certain laboratories although the diagnosis of NF-1 can be established according to the clinical stigmas. However, the investigation of clinical signs to get the clues for underlying mutation in all patients presented with PPGLs, which is so important particularly in NF1-positive patients [1]. Several tumor characteristics such as biochemical phenotype, tumor location, and histological evaluation could help to prioritize molecular testing for patients without family history and syndromic features.

Under the highlight of microarray studies PPGLs have been broadly distributed into two clusters according to the expression profiles. Cluster 1 includes pseudohypoxia-driven tumors displaying *VHL*, *SDH*, *EGLN1* and *HIF2A* mutations. Cluster 2 includes the kinase signalling tumors that have *RET*, *NF1*, *KIF1B*, *MAX*, *TMEM127* and presumably *H-RAS* mutations. Sporadic tumors are in between these two clusters [19,20].

The mutated gene *SDHB* was found the most common and endowed with the highest risk of malignancy [21]. It was detected in 30% of metastatic PPGLs. Patients with *SDHB* mutations are diagnosed at younger ages and are also associated with thoracic or abdominal extra-adrenal PPGLs [22]. The predominant biochemical typing is hypersecretion of dopamine or dopamine and norepinephrine. Also, increased levels of 3-methoxytyramine could help to diagnose *SDHB* mutation or other malignant tumors. Multiple tumors are found in *SDHB* carriers, however the penetrance of these mutations is low, so these patients could not be diagnosed until tumor detection. *SDHC*, *SDHAF2* and *SDHA* mutations are rare, so clinical evidence is limited.

*SDHC* mutations are benign and frequently associated with multiple head and neck tumors; the same applies to *SDHAF2* mutations at a similar age for sporadic tumors. Renal cell carcinoma, papillary thyroid carcinoma, pituitary adenoma, Carney-Stratakis dyad, and Carney triad have also been associated with *SDH* mutations. Current evidence suggests that *SDH* mutations may clinically arise as a metabolic tumor syndrome [5]. Therefore, *SDH* carriers who lack a positive family history for PPGLs should be inquired about the presence of *SDH* related tumors such as pituitary adenoma and renal cell carcinoma.

Germline mutation in the *RET* proto oncogene is the underlying mutation in multiple endocrine neoplasia (MEN) type 2A and 2B. Inheritance is autosomal dominant in MEN2 with high penetrance. However, genetic variations related *RET* proto-oncogene cause subtle changes in clinical presentation. Pheochromocytomas seen in MEN2 are almost always benign, frequently bilateral, adrenal and hypersecrete metanephrine.

NF1 is an autosomal dominant disease due to an inactivating mutation in the tumor suppressor gene named *NF1*. 50% of PPGLs in NF1 are familial and the rest are de novo mutations. PPGL is a rare component of NF1 that generally presents in the fourth or fifth decade and many patients also develop cutaneous manifestations. They usually present in a benign fashion with unilateral adrenal gland involvement, however, 12% of PPGLs can be malignant and occasionally bilateral.

VHL syndrome is a rare autosomal dominant syndrome classified according to the likelihood of developing PPGLs. Patients with VHL type 1 have a low risk of developing PPGL while type 2 have an increased risk. VHL type 2 sub-classifies into 3 groups: Type 2A is termed pheochromocytoma with low incidence of renal cell carcinoma (RCC), 2B is termed pheochromocytoma with high incidence of RCC, and 2C is termed sporadic PPGL. PPGLs in VHL patients are frequently benign, intraadrenal and bilateral. Also mediastinal, abdominal and pelvic sympathetic paragangliomas and head and neck parasympathetic paragangliomas have been reported. VHL patients have increased normetanephrine levels in contrast to those with NF1 and MEN-2 mutations.

Current evidence showed additional rare genes associated with development of PPGLs. The tumor suppressor gene *TMEM127* linked with mTOR kinase pathway has been found in relation with pheochromocytoma development. *MAX* protein functions as both an activator and suppressor gene associated with oncogenic pathways. However, which mechanism causes the PPGL is unclear. Tumors can be either adrenal or extra-adrenal and adrenal tumors are often bilateral and in malign behaviour. *KIF1β* is a rare germline mutation associated with PPGL and neuroblastoma. *EGLN1*, also named *PHD2* gene mutations cause familial paraganglioma through pseudohypoxic mechanisms. Loss of function of *FH* leads to the activation of pseudo-hypoxia driven pathways as in *SDH* mutations. *MDH2* mutation causes a deletion in the tumor suppressor gene leading to the inhibition of the HIFα pathway and malignant PPGLs. *HRAS* and *HIF2α* are well known somatic mutations that cause PPGL.

## Imaging

**Anatomic imaging:** Although imaging studies are recommended once a clear biochemical evidence is found, clinicians should be aware that skull base and neck paragangliomas and paragangliomas in patients with *SDHx* mutations can be biochemically negative. Hence, such tumors can only be detected by imaging studies.

**Tomography:** Computed Tomography (CT) is the first recommended imaging modality for detection of PPGLs because it offers excellent spatial resolution for thorax, abdomen and pelvis. PPGLs can have different appearance (homogeneous or heterogeneous, solid, complex or cystic) on CT. Larger tumors tend to have necrosis, and hemorrhage. Calcifications may be found in 10% of cases. Nearly all pheochromocytomas have an attenuation value of greater than 10 HU [23]. But pheochromocytomas that contain small amounts of fat can have attenuation values similar to adenomas measuring less than 10 HU [25]. On the other hand

the presence of hemorrhage can cause high density appearance. A tumour greater than 110 HU in the arterial phase is probably a pheochromocytoma. Additionally pheochromocytomas can mimic adenomas demonstrating absolute contrast washout values 60% or higher, or relative contrast washout values 40% or higher. Although contrast agents may precipitate a hypertensive crisis, nonionic ones are safe and therefore contrast CT can be performed in unmedicated patients. CT can detect tumors as small as 5 mm and most of these tumors are located in the abdomen therefore CT scan should be the first-choice imaging modality [1].

**Magnetic Resonance Imaging:** Magnetic Resonance Imaging (MRI) is recommended for patients with suspected skull base, head and neck paragangliomas, those with history of allergy to CT contrast agents or carrying surgical clips or suggested to avoid radiation (pregnant women, children, patients with germline mutation and those with recent radiation exposure). The classic MRI finding of PPGLs is a marked hyperintensity known as "light-bulb" bright lesion on T2-weighted images, but this sign can be detected in 11-65% of cases [26]. This is thought to be related to the difference between the amount of fluid contained in the cystic-necrotic and in the cellular homogenous areas of the tumour. PPGLs are characteristically isointense to muscle and hypointense as compared to liver on T1-weighted images. Pheochromocytomas characteristically exhibit avid enhancement after the injection of gadolinium but the presence of necrosis may change the enhancement pattern especially centrally. Diffusion-weighted imaging (DWI) is an imaging modality allowing insight into tissue cellularity and cell membrane integrity. Evaluation of DWI may have a role in distinguishing benign from malignant tumors during the preoperative evaluation [25].

Sensitivity of MRI ranges from 86 to 100%. But as with CT, possible false positive and false negative findings should be kept in mind to make differential diagnosis accurately.

## Functional Imaging

Functional imaging is important for detecting extraadrenal PPGLs, recurrent tumors and metastatic disease. <sup>123</sup>I- and <sup>131</sup>I-MIBG is the most common and available functional imaging modality used in the assessment of PPGLs. <sup>111</sup>In-Pentetreotide, 18F-fluorodopamine-, 18F-dihydroxyphenylalanine(DOPA) and 18F-fluorodeoxyglucose (FDG) are other radiotracers used for positron emission tomography (PET) functional imaging.

**<sup>123</sup>I- and <sup>131</sup>I-Metaiodobenzylguanidine:** Metaiodobenzylguanidine (MIBG) is concentrated by the sympathomedullary tissue through an active amine transport system and then stored in cytoplasmic vesicles. Pretreatment with Lugol iodine is recommended to saturate thyroid uptake and to prevent accumulation of MIBG in thyroid. The uptake of MIBG is proportional to the number of the vesicles within the tumor cells and characteristic appearance of the PPGL occurs.

Because imaging with <sup>123</sup>I- MIBG has a better sensitivity and a lower radiation exposure than <sup>131</sup>I-MIBG, only <sup>123</sup>I-MIBG is recommended for PPGLs imaging [26]. Also MRI and CT can be used in combination with <sup>123</sup>I-MIBG-single-photon emission computed tomography (SPECT) for better localisation.

Sensitivity of <sup>123</sup>I-MIBG has been reported between 85-88% for pheochromocytomas and between 56-75% for paragangliomas with a specificity of 70-100% and 84-100%, respectively. Affinity variations in the amine transport system, loss of amine transport system in dedifferentiated tumors and variations in the amount of cytoplasmic granules, presence of tumor necrosis may reduce its sensitivity [25]. Also the sensitivity of <sup>123</sup>I-MIBG in patients with *SDHB* related paragangliomas and skull base and neck, chest, bladder, metastatic disease and recurrent paragangliomas is low. Several drugs can decrease uptake of MIBG so these drugs should be withheld for 2 weeks before the procedure: 1) Sympathomimetics 2) Agents that block catecholamine transport through norepinephrine transporter such as tricyclic antidepressants, cocaine and 3) calcium channel blockers and combined α- and β-receptor blockers [1].

**<sup>111</sup>I-Pentetreotide:** PPGLs can sometimes express somatostatin

receptors which allows the use of pentetreotide (an analogue of somatostatin) for diagnosis. Pentetreotide is not used as first line diagnostic workup because of its low sensitivity but it may be used in the evaluation of MIBG-negative PPGLs that no longer express the amine transporter system and for detection of metastases [27].

**Positron Emission Tomography:** In recent years, PET has been widely available and used for diagnosis of PPGLs because of its high sensitivity. PET scan performed together with a corresponding CT increases the sensitivity. The Endocrine Society recommends using 18F-FDG PET/CT for assessment of known metastatic PPGLs [1].

Various radiotracers have been used for the diagnostic workup of patients with PPGLs. The most commonly used radiotracer is <sup>18</sup>F-FDG, an analogue of glucose that is taken up by the glucose transporter. A high standardised uptake value (SUV) reflects increased intracellular tumor metabolism thus allowing tumour detection. On the other hand caution should be exercised as FDG PET is not specific for PPGLs and many types of tumor may be detected by this technique. Several studies have demonstrated a superiority of FDG PET over MIBG scintigraphy for diagnosis of metastatic PPGLs particularly in patients with *SDHB* mutation [27,28].

Newer and more specific radiotracers have been developed. <sup>18</sup>F-Fluorodopa (FDOPA), a catecholamine precursor that is taken up through amino acid transporters, is specific for neuroendocrine tumors. Its sensitivity for diagnosis of head and neck paragangliomas is extremely high.

Another specific tracer is 18F-Fluorodopamine which is taken up with high affinity by norepinephrine transporters. Its high sensitivity for PPGLs supports its use in MIBG negative patients.

Studies with <sup>68</sup>Ga-labeled DOTA peptides (DOTATOC, DOTATATE and DOTANOC) have demonstrated a high sensitivity for neuroendocrine tumors including PPGLs [29]. However, these data are limited and tracers are not widely available for suggesting their routine use.

Current evidence showed that these tumors might exhibit a genotype-specific imaging phenotypes especially for those with germline mutations. It may be reasonable to use a stepwise imaging approach for PPGLs according to the genotype. For example, *VHL*-related PPGL cells express the cell membrane norepinephrine transporter system at lower rates than *MEN2*-related tumor cells [30]. Since MIBG has low affinity for these cells than <sup>18</sup>F-fluorodopamine, it is no surprise that <sup>18</sup>F-FDA PET is more sensitive than <sup>123</sup>I-MIBG scintigraphy in patients with *VHL*-related pheochromocytomas [31]. <sup>18</sup>F-FDG PET CT has a perfect sensitivity for *SDHB* positive metastatic PPGLs while <sup>123</sup>I-MIBG scintigraphy has much lower performance (about 50% or less) [32]. Increased FDG uptake may be related to *SDHB*-specific tumor biology rather than an increased metabolic rate [33].

## Malignant Pheochromocytomas and Paragangliomas

Despite several studies including demographic data, imaging modalities, genetic testing, microarray analysis, and immunohistochemistry were conducted to clarify this issue, there are no clear markers to predict which patients tend to develop metastatic disease during the management. Well known risk factors that increase malignancy risk are extra-adrenal location of the tumor, the size of the primary tumor, the presence of *SDHB* mutation, the age at primary tumor diagnosis, and increased levels of plasma methoxytyramine [34-37]. Moreover, distinguishing benign from malignant PPGLs and establishing the diagnosis of malignant PPGLs is particularly challenging in cases without metastatic lesions. Despite being more commonly seen in malignant tumours, PPGL capsular or vascular invasion is not a specific feature for malignancy [25].

## Pheochromocytoma in Special Conditions

### Pregnancy

PPGLs are rarely seen in pregnancy. Timely diagnosis is essential since it has a 40-50% mortality risk if untreated. Symptoms of PPGLs are similar to those observed in non-pregnant patients

such as hypertension, headache, sweating, and palpitations. Pheochromocytoma-related hypotension is also a common finding during pregnancy (40%) [38]. Women with hypertension-accompanied hypotension periods or severe hypertension onset before week 20 of gestation should be screened for pheochromocytoma. Also specific signs related to syndrome-based pheochromocytomas such as café-au-lait spots, freckles and fibromas need further investigation. Initially biochemical testing should be preferred before antihypertensive medication started, if possible. Catecholamine levels do not increase significantly and catecholamine metabolism does not change during pregnancy so the most sensitive test to establish diagnosis is the measurement of plasma free metanephrines and/or urinary fractionated metanephrines as in non-pregnant patients.

In pregnant women only ultrasonography and MRI can be used. Abdominal ultrasonography is rapid, cheap, and tolerable but it has low sensitivity especially in small tumors. MRI with gadolinium is another imaging procedure in these patients. Other diagnostic procedures such as CT, MIBG, other nuclear imaging modalities and biopsy are contraindicated in pregnancy because of their serious adverse effects [39,40].

### Renal failure

Pheochromocytoma should be considered in patients with symptoms of catecholamine excess, hemodynamic instability or when hypertension is unresponsive to therapy in renal failure. Measurements of urinary catecholamines and metabolites may not be useful in advanced renal failure. Additionally diagnostic specificity of chromogranin A is low. Patients under hemodialysis may have threefold and twofold elevated norepinephrine and dopamine levels respectively. Pheochromocytoma should be considered with plasma norepinephrine levels more than three fold the upper limit of normal and epinephrine levels above the upper normal range. According to the Eisenhofer et al, plasma concentrations of free metanephrines are relatively independent of renal function and may be more useful in the biochemical evaluation among patients with renal failure than measurements of deconjugated metanephrines [41]. A study including few cases found higher serum total metanephrines levels in patients with pheochromocytoma than in patients with or without hypertension, but they were not discriminatory after including patients with renal insufficiency [42, 43].

## Conclusions

PPGLs are relatively rare but potentially entrain life-threatening cardiovascular complications. Despite many recent advances in the field of PPGLs the delay in the diagnosis is still a problem and some of these tumours are unfortunately found at autopsy. Therefore true, timely and prompt diagnosis is very important. Before imaging studies, patients with PPGL symptoms, adrenal incidentaloma or known genetic predisposition, should undergo biochemical evaluation. As initial tests, analysis of plasma free metanephrines or urinary fractionated metanephrines are recommended because of their highest diagnostic performance. Blood samples should be collected under appropriate conditions and assay interferences should be taken into account to avoid false positive or negative results. Genetic testing is a critical component of the clinical evaluation of patients diagnosed with PPGLs so that current guidelines recommend genetic testing for all patients with PPGLs. Genetic testing of PPGLs helps to guide patient's management and provides early screening of patient's relatives in hereditary syndromes. After a biochemical diagnosis is established, anatomical imaging should be performed. Functional imaging is important for detecting extraadrenal PPGLs, recurrent tumors and metastatic disease. Clinicians should be aware of the presence of challenging cases during diagnostic workup and management follow particularly when dealing patients with chronic renal failure or pregnancy.

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